

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 05: Depression and Other Mental Health Disorders

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the three topics for which (1) preliminary mid- or late-phase data for drugs or behavioral therapies were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; and (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Nineteen topics in this priority area were being tracked in the system as of November 4, 2014.) We present summaries of three topics (indicated below by an asterisk) that emerged as having some potential for higher impact on the basis of expert comments. Topics in this Executive Summary and report are organized alphabetically. Readers are encouraged to read the detailed information that follows the Executive Summary.

Priority Area 05: Depression and Other Mental Health Disorders

Topic	High-Impact Potential
1. * Off-label ketamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
2. * Off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder	Moderately high
3. * Video game for cognitive behavior therapy for adolescents with major depressive disorder	Lower end of the high-impact-potential range

Discussion

Many of the interventions that the Healthcare Horizon Scanning System tracks in the mental health priority area are treatment alternatives for patients whose illness has not responded to available medications and behavior therapies for bipolar depression (BPD), major depressive disorder (MDD), or posttraumatic stress disorder. Recent research suggests that these disorders may involve abnormal modulation of multiple neurotransmitters, pathways, and receptors in the brain. Although the underlying neurobiology is still being investigated, new medications and behavioral therapies are attempting to address novel and previously examined mechanisms to provide therapies for both adult and adolescent patients.

Since the last High Impact report in June 2014, no new topics in this priority area were eligible for consideration for high-impact potential because no phase III were available on them. Thus, each of the topics included in this report was covered in the previous report. This report updates and discusses these interventions that experts determined to have high-impact potential for treating depressive disorders: two off-label pharmacotherapies and a software-based behavior therapy.

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** Despite numerous available U.S. Food and Drug Administration (FDA)-approved medications, many patients with BPD or MDD have disease that can be classified as medically refractory. Even among patients whose disease responds to prescribed medications, symptom improvement can be slow or incomplete. These inadequate responses place patients at sustained risk of severe symptoms, such as suicidal ideation; an unmet need exists for additional pharmacotherapy options for this patient population. Ideally, these alternatives would also act rapidly, enabling effective treatment in emergency events. Ketamine (racemic ketamine hydrochloride), an FDA-approved general anesthetic, is under investigation for rapidly treating medically-refractory BPD and MDD; ongoing basic research and clinical trials are being sponsored by multiple groups, including the National Institute of Mental Health. Researchers hypothesize that ketamine's antidepressant properties are likely due to its multiple neurobiological activities, including roles as a N-methyl-D-aspartate receptor antagonist and regulator of mitogen-activated protein kinase signaling pathways.

In clinical trials, single doses of ketamine at a dose far below that needed to achieve anesthesia are intravenously infused. Preliminary data suggest that in some patients, low-dose ketamine produces significant, rapid (within 2 hours), and relatively sustained (about 1–2 weeks long) improvement in depression symptoms. In small studies and case reports, intravenous ketamine administration also reduced suicidal ideation in depressed patients. Most ongoing clinical trials are investigating optimal doses and regimens of ketamine for specific patient populations. However, one manufacturer is studying esketamine, the purified (S)-enantiomer form of ketamine, for this indication, and preliminary research has suggested that ketamine's (R)-enantiomer may have antidepressant properties, without racemic ketamine's psychomimetic side effects.

The U.S. Drug Enforcement Administration classifies ketamine as a Schedule III drug, requiring a license and prescription to obtain. Ketamine's unpredictable psychomimetic side effects in some patients—including hallucinations, anxiety, and insomnia—could curb adoption by patients and clinicians. Some clinical practices report offering ketamine infusions for treating depression; patient blogs also report patient experiences and out-of-pocket costs of ketamine infusions for MDD. Reported fees from clinicians and patients range from \$525 to \$1,250 per infusion; patients reported that an intranasal formulation was much less costly. Although anecdotal reports suggest increased off-label ketamine use for treating mental health disorders, third-party payers do not cover it.

- **Key Expert Comments:** Experts commenting on ketamine for treatment-resistant major depression believe that ketamine has moderate potential as a rapid-acting, effective treatment for BPD and MDD. They noted that ketamine's intravenous delivery route could shift patient care settings from self-administered oral antidepressant therapy to clinician offices and infusion clinics. However, some experts noted that ketamine's cost, inconsistent

clinical trial results, and safety risks would hinder adoption; these experts suggested that additional long-term clinical trial data could address whether these concerns are warranted.

- **High-Impact Potential:** Moderately high

Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

- **Key Facts:** The significant economic and public health burdens associated with BPD and MDD have propelled research into pharmacotherapies with novel mechanisms of antidepressant action. Cholinergic pathways and dysfunctional cholinergic receptors are purported to underlie some symptoms of depression; these findings have prompted studies of anticholinergic medications as possible antidepressant therapies. Scopolamine is an anticholinergic agent, FDA-approved for treating peptic ulcers, motion sickness, and post-surgical nausea. Ongoing clinical trials led by researchers from Massachusetts General Hospital (Boston, MA) and the National Institute of Mental Health are investigating scopolamine for treating BPD and MDD.

In clinical trials, researchers have investigated antidepressant properties of intravenously infused, oral tablet, and transdermal patch scopolamine formulations. Preliminary data from multiple trials suggest that scopolamine functions as a rapidly acting antidepressant, potentially effective in treating patients with medically-refractory BPD or MDD.

No scopolamine manufacturers are sponsoring registered clinical trials for this indication. Although most clinical trials use intravenous scopolamine, only oral and transdermal patch formulations are available for retail purchase, with prices ranging from \$100 for a monthly supply of oral tablets to \$170 for 10 transdermal patches.

- **Key Expert Comments:** Experts evaluating this intervention thought that scopolamine has potential to address an unmet need for rapid-onset, effective treatment for BPD and MDD. They were also encouraged by scopolamine's prospective use as a monotherapy and as an addition to traditional selective serotonin reuptake inhibitors. Some experts noted that depending on the most effective administration route, scopolamine use could shift care settings toward outpatient infusion therapy. Experts also stated that insufficient clinical trial data and known anticholinergic side effects could limit scopolamine's adoption among clinicians.
- **High-Impact Potential:** Moderately high

Video Games for Cognitive Behavior Therapy for Adolescents with Major Depressive Disorder

- **Key Facts:** Standard nonpharmaceutical treatments for adolescents with early-onset major depressive disorder (eoMDD) include supervised individual or group cognitive behavior therapy (CBT) sessions. Many adolescent patients find these sessions unpleasant; subsequently, they build entrenched negative associations and fail to adequately seek, engage, and adhere to treatment. An unmet need exists for effective, appealing, outpatient, treatments for adolescent patients with eoMDD. SPARX™ is a first-in-class, video game-based software, developed in New Zealand and intended for outpatient treatment of adolescents with eoMDD. The approach integrates traditional CBT concepts with an immersive, self-directed virtual environment modeled on popular role-playing “quest” games.

In published clinical trials, patients completing SPARX game modules reported significantly reduced depressive symptoms compared with symptoms of patients receiving traditional in-person therapy sessions. SPARX patients reported high adherence rates with favorable perceptions of the software. Clinical trials are ongoing, and the software has been adapted for use with specialized patient subgroups.

LinkedWellness has licensed SPARX for commercial sale in North American markets; American patients can download a full beta version from LinkedWellness' Web site. SPARX is also a featured component of New Zealand's Youth Mental Health Project and has been used by more than 1,500 New Zealanders since April 2014.

- **Key Expert Comments:** Overall, experts were impressed by SPARX's design quality and stated that it effectively addresses a significant unmet need for patients with eMDD. Experts thought that SPARX could positively improve patient health outcomes without placing significant burden on health care delivery infrastructure because the software functions as a private, outpatient intervention requiring limited clinician oversight. They noted that as a video game-based intervention, SPARX could be widely adopted by patients and their parents. Experts also believe that SPARX might reduce disparities in intervention access associated with traditional behavior therapies. Although comments were generally positive, experts expressed a need for additional clinical trial data from patients outside New Zealand to demonstrate viability and efficacy, particularly considering pending commercialization in North America.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Depression and Other Mental Health Disorder Interventions

Off-Label Ketamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Many patients in whom bipolar depression (BPD) or major depressive disorder (MDD) has been diagnosed do not respond well to approved medications.¹ Existing medications also do not act rapidly to alleviate depression symptoms, rendering them ineffective for treating acute episodes where immediate intervention is required to minimize severe risk of patient self-harm.^{1,2} Additionally, many standard MDD and BPD pharmacotherapies have significant side effects and are unacceptable options for some patients.¹ An unmet need exists for effective, fast-acting, well-tolerated medications for treatment-resistant BPD or MDD. Ketamine, a widely used general anesthetic, may offer an effective, off-label option for these patients.

Intervention: Ketamine is a racemic, noncompetitive, high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist, approved by the U.S. Food and Drug Administration (FDA) for use as a general anesthetic.^{1,3} NMDA is a global receptor for glutamate, the major excitatory neurotransmitter, and it also functions as a primary mechanism for controlling synaptic plasticity.^{1,4} Recent studies implicate dysfunctional glutamate neurotransmission as a principal cause of depressive symptoms in MDD and BPD, although the exact mechanism of action is unclear.^{1,4,5} Converging evidence also suggests that NMDA receptor signaling may mediate glutamate dysregulation, leading some researchers to hypothesize that NMDA antagonists could possess potent antidepressant effects.^{5,6}

Preliminary neurobiological studies suggest that ketamine's antidepressant effects are driven by its roles in synaptic plasticity and synaptogenesis. Specifically, ketamine-mediated increases in brain-derived neurotrophic factor (BDNF) levels are hypothesized to activate mammalian target of rapamycin (mTOR) and inhibit eukaryotic elongation factor 2 kinase.^{4,7-10} Modulation of these two targets may underlie a majority of ketamine's observed antidepressant activity.^{10,11}

Nascent research suggests that ketamine's enantiomers, (S)- and (R)-ketamine, may also be potent antidepressants and may have fewer side effects than racemic ketamine. Presently, (R)-ketamine studies are limited to animal models. However, a Johnson & Johnson subsidiary is in early development stages for an intranasal form of purified S-ketamine, also known as esketamine, for treating depression indications.¹²

In clinical trials for treating MDD and BPD, investigators intravenously or intramuscularly inject ketamine at subanesthetic doses. Across published reports, the most common dosing protocol is a single, 0.5 mg/kg intravenous injection. Smaller clinical trials and case reports indicate that oral, intranasal, and rectal ketamine formulations may also effectively treat depression symptoms.^{13,14} Intravenous ketamine has also been investigated as an adjunct medication to electroconvulsive therapy (ECT) for treatment-resistant MDD.

Clinical trials: Multiple ongoing clinical trials are investigating off-label ketamine for treatment-resistant depression in both adolescents and adults with BPD or MDD.¹⁵⁻²⁰ Additional trials and case studies are also expanding into research on ketamine's treatment efficacy for suicidal ideation and as an adjunct treatment to behavior and brain-stimulation therapies.^{21,22} Completed studies have repeatedly reported positive, rapid, and long-lasting antidepressant effects of single intravenous ketamine infusions in these patient populations, with the majority of results from patients with MDD.^{1,2,18,23} Results from studies using repeated ketamine doses have been less consistent, though, with reports suggesting that efficacy may vary across patients and depend on symptom severity and infusion protocols.²⁴⁻²⁷

In 2014, two research groups independently conducted systematic reviews and meta-analyses of published literature reporting ketamine administration for treating MDD and BPD. The first review

concluded that ketamine treatment was associated with higher rates of clinical remission and response when compared with placebo or a comparator anesthetic.²⁸ This finding was consistent for patients with BPD or MDD and among patients receiving ketamine paired with ECT.²⁸ The second review confirmed similar ketamine efficacy among groups examined in the first report and also found significant, treatment-based improvement for patients with treatment-resistant disease (i.e., those who failed to respond to one or more alternative antidepressant medications).²⁹

Multiple small studies have reported that intravenous ketamine, when administered to patients in whom BPD has been diagnosed, produces significant improvements in depressive symptoms and suicidal ideations within 40 minutes compared with placebo. In one study, National Institute of Mental Health (NIMH) investigators reported that 79% of patients with BPD (n=15) responded positively to ketamine.² These same investigators observed that ketamine also treated anhedonia (diminished pleasure from, or interest in, previously rewarding activities) symptoms; patients with BPD (n=36) showed rapid reductions in anhedonia after a single ketamine administration.³⁰ A separate Polish clinical trial enrolling hospitalized adult patients with treatment-resistant BPD (n=25) found that intravenous ketamine administration was well tolerated and resulted in rapid and sustained improvements in depression severity, based on standard rating scale scores.¹⁹

Adverse-event reporting is not available from all clinical trials, but one systematic review of ketamine administration in patients with MDD reported that treatment-related adverse events were generally mild, with some patients experiencing brief, reversible changes in blood pressure, heart rate, or respiratory rate.³¹ However, some case reports have observed severe adverse events, including delayed-onset suicidal ideation, dysphoria, and anxiety.³²

The largest clinical trials to date (with enrollments between 100 and 324 patients) are ongoing, investigating ketamine's efficacy for treating MDD, BPD, and comorbid suicidal ideation.³³⁻³⁵ Trials are also investigating the efficacy of repeated ketamine administrations in treating depressive disorders, and trials are studying biomarkers that might predict patient response to ketamine for these indications. Two clinical trials, investigating optimal doses of intranasal esketamine for MDD and efficacy for treating depressed patients at high risk of suicide, are also registered.^{36,37}

Manufacturer and regulatory status: FDA has approved ketamine for use as an anesthetic for diagnostic and surgical procedures. It is available in generic form from several manufacturers, as well as in branded form, as Ketalar® (JHP Pharmaceuticals, LLC, Parsippany, NJ). Ketamine is not approved for treating BPD or MDD, and no manufacturers are sponsoring clinical trials in pursuit of expanded labeling.

Janssen Research & Development (a subsidiary of Johnson & Johnson, New Brunswick, NJ) is developing intranasal esketamine for treating MDD and treatment-resistant MDD. FDA has granted fast-track status to esketamine for this indication, and Janssen plans to also apply for breakthrough therapy status.^{38,39} Janssen has two new phase II trials registered for these indications.^{36,37}

Diffusion and costs: Ketamine is classified as a Schedule III controlled substance and cannot be purchased and administered without a U.S. Drug Enforcement Administration license.^{40,41} Higher-dose ketamine is colloquially known as “Special K” and is sometimes abused as a street drug, further hampering attempts to expand approvals and availability for off-label use.^{42,43}

Among research groups sponsoring ketamine clinical trials for BPD and MDD are Columbia University (New York, NY), Massachusetts General Hospital (Boston, MA), the New York State Psychiatric Institute (New York, NY), and the National Institute of Mental Health (NIMH; Bethesda, MD).⁴⁴⁻⁵¹ NIMH and Massachusetts General are primary collaborators of the two largest ongoing trials.^{34,51}

Searches of clinical practice Web sites found multiple locations offering off-label ketamine infusions for treating depression; patient blogs also report patient experiences and out-of-pocket costs of ketamine infusions for MDD. Reported per-infusion costs ranged from \$525 to \$1,250;

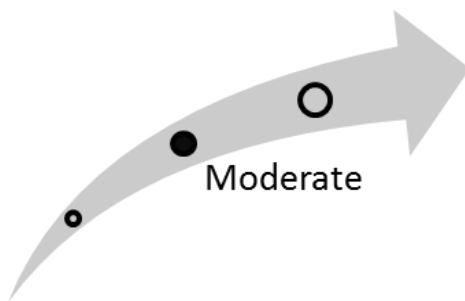
patients reported that an intranasal formulation was much less costly.⁵²⁻⁵⁵ Anecdotal evidence also suggests that off-label prescribing of ketamine for MDD has been increasing.⁵⁶

Clinical Pathway at Point of This Intervention

Various pharmacotherapy and group and individual psychotherapy are standard treatments for BPD and MDD. Common antidepressants for MDD include atypical antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs); these medications are used in both monotherapy and combination therapy.⁵⁷⁻⁵⁹ Anticonvulsants, antipsychotics, benzodiazepine, and lithium are standard medications for treating BPD.⁶⁰ Additionally, clinicians may also use ECT, forms of transcranial magnetic stimulation (TMS), or implanted vagus nerve stimulation to treat patients with treatment-resistant depression.^{59,60}

Ketamine has a different mechanism of action and molecular targets from alternative depression pharmacotherapies; as a result, ketamine may complement other interventions. Some clinical researchers predict that ketamine, as a rapid-acting antidepressant, can serve as a possible therapeutic bridge until standard antidepressants take effect.

Figure 1. Overall high-impact potential: off-label ketamine for treatment-resistant bipolar depression and major depressive disorder



Experts commenting on this topic thought that ketamine has some potential as a rapid-acting, effective treatment for BPD and MDD. If intravenous delivery is the most effective administration route, ketamine adoption could shift patient care settings toward clinician offices and infusion clinics, the experts also thought. They were encouraged by reported clinical trial data demonstrating broad efficacy, but noted a dearth of robust clinical trials. Adoption could be limited by ketamine's cost, inconsistent clinical trial data, and safety risks, multiple experts also opined. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, health systems, and research backgrounds, provided perspectives on off-label ketamine for treating MDD and BPD.⁶¹⁻⁶⁶ We have organized the following discussion of expert comments by the parameters on which experts commented; expert comments generally evaluated intravenous ketamine infusions for treating BPD and MDD, because this administration route is more established than other administration routes for these indications.

Unmet need and health outcomes: Alternative pharmacotherapies for treatment-resistant BPD and MDD constitute a moderate to significant unmet need, the experts thought. Their consensus opinion was that ketamine could address a need for rapid-acting pharmacotherapies for these indications. Several experts thought that intravenous ketamine would have a moderate-to-large impact on health outcomes for these treatment-resistant cases. But one expert with a research

background, citing ketamine's safety risk and lack of long-term efficacy data, disagreed and believes that ketamine will not meet this need.⁶⁴

Acceptance and adoption: Opinions concerning anticipated acceptance and adoption were divided. Several experts, focusing on immediate patient and clinician adoption, predicted that acceptance would be limited; these experts cited ketamine's safety risks and lack of robust clinical trial data as constraining factors. However, predicting additional efficacy data and resolution of potential adverse effects, two experts concluded that clinician and patient acceptance and adoption rates would be high; additionally, they stated that ketamine would be preferred to TMS and ECT for these indications.^{62,65}

Health care delivery infrastructure and patient management: For these indications, ketamine administration would result in minimal disruption of health care delivery infrastructure and patient management, the experts thought. Experts also stated that this intervention would require increased patient monitoring and must be administered by trained clinicians. However, two experts noted that if oral or intranasal ketamine formulations were adopted, these infrastructure needs would be reduced.^{63,66}

Health Disparities: This intervention has little potential to positively impact health disparities, the experts thought. Several experts noted that if widely adopted as an off-label treatment, ketamine costs could be comparable to TMS and ECT interventions.^{65,66} These treatment options are acknowledged as relatively expensive, later-line therapies; a similarly priced intervention may not be widely accessible to patients with limited financial resources.

Off-Label Scopolamine for Treatment-Resistant Bipolar Depression and Major Depressive Disorder

Unmet need: Patients in whom treatment-resistant or medically-refractory BPD or MDD has been diagnosed need additional, effective therapies to improve their symptoms.¹ Many available pharmacotherapies are slow-acting and poorly tolerated. These medications are not viable options for managing acute depressive episodes, particularly cases involving concomitant suicidal ideation.^{1,2} An unmet need exists for effective, fast-acting, and well-tolerated medications for treating medically-refractory BPD or MDD. If proved effective, scopolamine may meet this need, either as a monotherapy or adjunct medication.

Intervention: Scopolamine is a belladonna alkaloid with strong anticholinergic properties, functioning as a competitive inhibitor at muscarinic acetylcholine receptors (mAChRs).⁶⁷ Although the mechanism of central nervous system cholinergic dysfunction in depression is not completely elucidated, data suggest that increased cholinergic pathway activity contributes to the negative emotional-processing bias observed in many mood disorders.⁶⁸ Research has implicated the central nervous system–cholinergic system in the pathophysiology of depressive disorders, and studies have identified mAChRs genetic variants linked to increased risk of developing depression.⁶⁹ Recent animal model studies also demonstrated explicit M1 and M2 muscarinic receptor subtypes that regulate scopolamine’s antidepressant activity.⁷⁰

Scopolamine is hypothesized to mediate cholinergic system hyperactivity in patients with depression, potentially restoring normal emotional processing and easing depressive symptoms.⁶⁹ Clinical data suggest that these changes may occur within 3 days of treatment, making scopolamine a faster-acting antidepressant option than available pharmacotherapies.^{71,72}

In clinical trials for treating MDD and BPD, clinicians often administer scopolamine intravenously. The most frequently reported dosing protocol involves three 4 mcg/kg infusions, spaced 3–5 days apart.^{69,73} Alternatively, one trial has investigated a twice-daily 0.5 mg oral scopolamine dose, administered with citalopram.⁷² NIMH is also sponsoring an ongoing clinical trial investigating the antidepressant efficacy of a transdermal scopolamine patch.⁷⁴

Clinical trials: In 2012, a phase II/III trial enrolling patients with MDD (n=40) found that intravenous scopolamine, administered adjunct to citalopram, was more effective than placebo at increasing rates of response (65% vs. 30%, p=0.027) and remission (65% vs. 20%, p=0.004).⁷² Scopolamine’s antidepressant efficacy was confirmed in a separate clinical trial with patients in whom MDD or BPD had been diagnosed (n=52); this study also found larger treatment effect sizes among female patients than among males.⁷³ Additionally, a recent systematic review concluded that all available scopolamine formulations had some degree of antidepressant efficacy.⁷⁵

In the phase II/III trial, scopolamine infusions were associated with increased incidence of blurred vision, dizziness, and dry mouth.⁷² For scopolamine’s approved indications, commonly observed infusion-related adverse events include pharyngitis, tachycardia, and urinary retention; severe, but less frequently observed severe adverse infusion-related events include confusion, agitation, hallucinations, paranoid behaviors, and delusions.^{67,76,77}

Three registered clinical trials are ongoing for this off-label indication. These trials include a large study (n=388) examining transdermal scopolamine’s antidepressant efficacy.⁷⁴

Manufacturer and regulatory status: Intravenous scopolamine has FDA approval for use as a sedative and antiemetic, and it is available in generic and branded formulations.⁶⁷ Oral scopolamine (methscopolamine bromide) is an FDA-approved, adjunct treatment for peptic ulcer disease; it is also available in generic and branded forms.^{77,78} Novartis International AG (Basel, Switzerland) also manufactures a transdermal extended-release scopolamine patch, branded as Transderm Scōp.

Scopolamine's manufacturers are not actively engaged in clinical trials investigating its use for treating MDD or BPD. In the absence of formal development programs, scopolamine use is off label for depression indications.

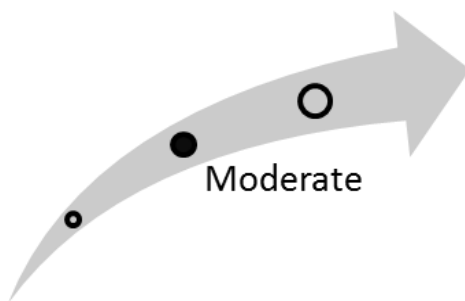
Diffusion and costs: Unlike ketamine, off-label scopolamine use for treating MDD and BPD has not significantly diffused beyond clinical trials; Massachusetts General Hospital and NIMH are sponsoring three clinical trials investigating off-label scopolamine for these indications. Accordingly, this intervention's anticipated per-patient and per-treatment costs are unknown. Oral and transdermal patch scopolamine, however, are available for purchase with a prescription. One month's worth of methscopolamine bromide tablets costs about \$100, while a similar supply of transdermal patches costs approximately \$170.^{79,80}

Clinical Pathway at Point of This Intervention

Various pharmacotherapies and group and individual psychotherapy are standard treatments for BPD and MDD. Common antidepressants for MDD include atypical antidepressants, monoamine oxidase inhibitors, and SSRIs; these medications are used in both monotherapy and combination therapy.⁵⁷⁻⁵⁹ Anticonvulsants, antipsychotics, benzodiazepine, and lithium are standard medications for treating BPD.⁶⁰ Additionally, clinicians may also use ECT, forms of TMS, or implanted vagus nerve stimulation to treat patients with treatment-resistant depression.^{59,60}

As a muscarinic cholinergic receptor antagonist, scopolamine has a mechanism of action novel among approved and experimental antidepressant medications. This uniqueness could allow scopolamine to be used as a monotherapy and complementary pharmacotherapy; preliminary findings using combined scopolamine and citalopram suggest that scopolamine may be an effective adjunct to multiple SSRIs. Additionally, as an antidepressant with a rapid onset akin to ketamine, clinicians could administer scopolamine as a transitional medication alongside slower-acting medications, TMS, ECT, or psychotherapy.

Figure 2. Overall high-impact potential: off-label scopolamine for treatment-resistant bipolar depression and major depressive disorder



Experts assessing this topic expressed optimism for scopolamine's potential as a safe, effective, rapidly-acting intervention for patients with treatment-resistant BPD and MDD. With further clinical trial evidence, experts stated, scopolamine could be adopted by some patients and clinicians. If intravenous scopolamine has superior efficacy, experts thought, its use would have some impact on health care delivery infrastructure and care settings, shifting some patients from self-administered oral medication to infusions administered in clinical settings. Additionally, experts acknowledged that off-label use may limit adoption, because third-party payers may not initially cover scopolamine treatment for these indications. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Five experts, with clinical and research backgrounds, commented on off-label scopolamine for this indication.⁸¹⁻⁸⁵ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: All consulted experts agreed that treatment-resistant BPD and MDD cases represent a substantial public health need, necessitating new, effective interventions. However, experts' consensus opinion also held that clinical trial data supporting scopolamine use for these indications are significantly lacking. Two clinical experts noted that until additional supporting data are available, scopolamine would remain a promising potential antidepressant but will have little impact on patient health outcomes.^{83,84}

Acceptance and adoption: Despite its potential efficacy, scopolamine will have low to moderate acceptance and adoption among patients and clinicians, the experts anticipated. Experts suggested that this limited predicted diffusion is primarily due to insufficient clinical trial data. In contrast, scopolamine's known safety profile and possible oral and patch delivery options, bolstered by further positive clinical data from larger ongoing trials, could drive additional acceptance.⁸³⁻⁸⁵

Health care delivery infrastructure and patient management: Oral and transdermal scopolamine formulations would minimally impact health care delivery infrastructure and patient management, the experts generally thought. Intravenous scopolamine, though, could be more disruptive, because it requires more patient management and administration at clinics or infusion centers. Two experts, however, considered that if intravenous scopolamine is consistently rapid-acting and involves only periodic maintenance administration, additional patient management and delivery infrastructure burdens would be nominal.^{83,84}

Health Disparities: Experts were divided in their evaluations of scopolamine's potential health-disparities impacts. All consulted experts noted that as an off-label medication, scopolamine's cost was a key component in determining health-disparities impacts. Some experts concluded that this cost would not be a significant burden to patients with reduced financial means.^{81,83,85} Other experts thought that, especially if used as an adjunct to other treatment, scopolamine's added cost may decrease patients' access to this intervention.^{82,84}

Video Game for Cognitive Behavior Therapy for Adolescents with Major Depressive Disorder

Unmet need: Early-onset major depressive disorder (eoMDD) has a high prevalence among adolescents and can lead to additional depression symptoms as patients age. Although traditional cognitive behavior therapies (CBTs) can effectively treat mild to moderate eoMDD cases, many patients fail to seek or receive treatment. Survey data indicate that even among adolescents who self-identify as needing mental health intervention, fewer than 20% use available services.⁸⁶⁻⁸⁸ An unmet need exists for effective, engaging treatments for this patient population. SPARX is a self-directed computerized CBT (cCBT) program, intended to address this need, offering a therapeutic alternative with increased ease of access and lower associated stigmas than traditional eoMDD treatments.

Intervention: SPARX (Smart, Positive, Active, Realistic, X-factor) is a thoughts-depression-intervention software consisting of seven individual modules, modeled after role-playing “quest” games.⁸⁹ SPARX functions as a self-directed cCBT, designed mainly for use by adolescents with eoMDD. The software is based upon traditional cCBT techniques, teaching and reinforcing strategies for identifying and addressing negative thoughts and feelings.⁸⁹

During gameplay, patients select an avatar, used to interact with the game environment. Other in-game characters including a “guide” avatar, who introduces and reviews cCBT techniques at the start and finish of each module. Guide avatars also regularly query patients’ moods and recommend that patients who are not improving seek additional treatment options beyond SPARX. Each module takes approximately 30 minutes to complete, and patients are instructed to complete one to two modules weekly.⁸⁹ Developers expect that all modules can be finished within 4–7 weeks.⁹⁰ SPARX’s developers suggest that patients maintain a notebook while completing the software, as a means of tracking their moods and progress. Clinical trial versions of SPARX also allowed supervising clinicians to monitor patients’ progress via an online monitoring system.⁸⁹

SPARX software purportedly serves as a self-paced primary treatment option for patients with eoMDD or an adjunct to other therapies. Patients who may otherwise not pursue treatment could find this intervention more tolerable than other options. SPARX’s developers expect that the software can be used in patient’s homes; in schools, with or without trained counselor or clinician oversight; and in clinician offices, as an adjunct to directed psychotherapy.

Clinical trials: In completed and ongoing clinical trials, researchers use Child Depression Rating Scale (CDRS) scores as a primary intervention assessment measure. Sixty-six adolescent patients with MDD were studied in two clinical trials; patients were randomly assigned to either the SPARX intervention or standard, in-person CBT. SPARX was well received and demonstrated high intervention adherence (81% and 94%; adherence defined as patients completing at least 4 of 7 modules in the first trial and completing all modules in second trial).^{91,92} Patients who completed SPARX also demonstrated significantly greater symptom improvement than did patients receiving standard CBT.^{91,92}

In a separate clinical trial, treatment-seeking adolescent patients (n=187) were randomly assigned to complete SPARX or standard in-person CBT. Treatment-seeking adolescents who completed SPARX had larger mean CDRS score reductions (10.32 vs. 7.59, $p=0.079$) and statistically significantly higher remission rates (43.7% vs. 26.4%, $p=0.030$) than patients receiving standard CBT.⁸⁹

SPARX’s developers have also customized a version for treating adolescent patients with depressive symptoms who also identify as members of sexual minority groups (i.e., adolescents sexually attracted to the same sex, both sexes, or who are questioning their sexuality). Preliminary

data for this intervention were reported in April 2014. Patients who finished this tailored intervention demonstrated statistically significant, sustained decreases in depressive symptoms ($p < 0.0001$, effect size $d = 1.01$; decreases were maintained at 3-month followup).⁹³

This intervention's largest clinical trial to date ($n = 3,500$) is ongoing in Canada, investigating SPARX's efficacy as a monotherapy and adjunct to traditional CBT for treating hazardous alcohol use and depressive disorders.^{94,95}

Manufacturer and regulatory status: The SPARX software development was led by researchers, headed by Dr. Susan Merry, in the University of Auckland's (Auckland, New Zealand) Department of Psychological Medicine. The University's commercialization arm contracted an exclusive North American licensing agreement with LinkedWellness (Baltimore, MD).⁹⁶

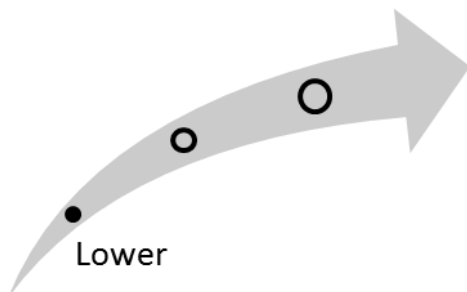
Diffusion and costs: North American patients can download a free, fully functioning beta version of SPARX through LinkedWellness' Web site. Available versions work in Chrome and Safari browsers and Android mobile device environments; an iOS-compatible mobile device version is forthcoming.⁹⁷ Neither the original developers nor LinkedWellness have reported diffusion data for this patient population.

In New Zealand, SPARX was identified as a centerpiece of the prime minister's Youth Mental Health Project.^{98,99} As part of this initiative, the Australian and New Zealand governments are supporting SPARX's diffusion with more than \$17 million in funding.¹⁰⁰ Since its public release in April 2014, more than 1,500 adolescent New Zealanders have accessed the software through various New Zealand-based Web sites.^{101,102}

Clinical Pathway at Point of This Intervention

Clinicians use physical and psychological examinations to confirm an eMDD diagnosis. Adolescent patients can be treated with psychotherapy, one or more antidepressants, or combination therapies. SPARX may be used as an outpatient monotherapy or in combination with other standard treatments.⁸⁹

Figure 3. Overall high-impact potential: video game for cognitive behavior therapy for adolescents with major depressive disorder



Overall, experts assessing SPARX were somewhat optimistic about its potential to address an unmet need for effective, well-tolerated eMDD interventions. Experts thought that SPARX offered a valuable behavior intervention in an engaging format that could promote broad acceptance by patients hesitant to pursue alternative eMDD treatments. Although experts remarked that available clinical trial data were favorable, they noted a need for additional efficacy data, particularly to confirm SPARX's efficacy for non-New Zealanders, whose culture backgrounds and treatment needs might differ. Experts also concluded that SPARX would not increase health care delivery infrastructure or patient management burdens and would be adopted by clinicians seeking efficient therapeutic options for their patients. However, they also acknowledged that because SPARX does not prevent eMDD, this intervention may have limited potential to improve patient health

outcomes. Based on this input, our overall assessment is that this intervention is at the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, health systems, and research backgrounds, offered perspectives on this intervention.¹⁰³⁻¹⁰⁸ We have organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: eoMDD is an important and growing health issue, the experts agreed; they concluded that SPARX could address an unmet need for effective, well-accepted interventions for this indication. Untreated patient rates could also decline if SPARX diffuses; experts stated that this factor could contribute to SPARX positively affecting patient health outcomes.

Acceptance and adoption: Experts anticipated wide acceptance and adoption among patients, who will likely consider SPARX as a more entertaining treatment option with less associated social stigma and fewer side effects than other interventions. One expert with a health systems background viewed SPARX demonstration videos online, lauded their design quality in comparison to nontherapeutic commercial video games, and forecast patients being receptive to SPARX as an eoMDD treatment.¹⁰⁶

Although patients may readily adopt SPARX, projected acceptance and adoption among clinicians would be moderate, the experts thought. They remarked that further clinical trial data are needed to stimulate wide acceptance among clinicians and other mental health care providers. One expert with a research background mentioned that individual clinicians' acceptance might also be contingent on whether they foresee SPARX as monotherapy option or as a supplemental intervention.¹⁰⁴

Health care delivery infrastructure and patient management: As a computer-based outpatient intervention, SPARX would minimally affect health care delivery infrastructure and patient management, the experts agreed. Experts also noted that diffusion could shift some proportion of primary treatment towards patients' homes or schools, rather than towards clinician offices and behavior-therapy facilities.

Health Disparities: Experts anticipated that SPARX would minimally impact health disparities, but provided multiple justifications. Some experts noted that making eoMDD treatment available to any patient with computer access could reduce disparities. Two experts explicitly noted that SPARX is available only in English, limiting its efficacy among non-English-speaking patients.^{106,108} Additionally, some experts noted that although the beta version is freely available online, after full commercialization, SPARX may be too expensive for economically disadvantaged patients.

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